Clinical Review

Psychotropic Medication Use During Pregnancy

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Women can have severe and at times life-threatening psychiatric illness during pregnancy. When nonpharmacologic interventions have been attempted and are insufficient, psychotropic medication use is often necessary. The available data on prescription neuroleptic drugs suggest that with the proper selection, use, and supervision, they can be used during pregnancy. The same cannot be said for lithium carbonate or most antidepressants owing to the risks of teratogenicity and toxicity to the fetus. It is prudent to avoid all medication use, if possible, during the first trimester, but deciding how and when to institute treatment depends on an assessment of the risks associated both with the drug and with the untreated illness.

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Those who treat pregnant women are, under most circumstances, cautious in their use of prescribed medications. On occasion, however, a woman taking psychotropic medication will discover that she has become pregnant. At this time she may ask her physician for advice concerning the relative risk to her unborn child. A patient's concern may include both the risk from previous exposure and the possible risk to the fetus from continued exposure.

In addition, when a serious mental disorder arises in a pregnant patient and nonbiologic methods such as individual, couple, or family psychotherapy, social casework, or admittance to hospital have been exhausted, it is often necessary to consider pharmacologic methods of treatment. If the risks associated with using psychotropic drugs are outweighed by the anticipated benefits and if the risk of inadequately treated disease outweighs that associated with a potentially useful medication, then most prudent physicians will opt to treat the disease. The dilemma for clinicians, however, is that no psychotropic drug has been proved safe for use during pregnancy and all carry warnings from the Food and Drug Administration.

Before prescribing a drug during pregnancy, many factors should be considered, including the effects of the drug during labor, the withdrawal effects on the newborn, if any, and the possibility that the medication will cause some form of congenital malformation. In addition, many consider it prudent to consult with a specialist in psychopharmacology before administering these drugs to pregnant women.

In this review we examine the risks to infants of in utero exposure, congenital malformation, and the possible postpartum effects of the use of lithium carbonate, antidepressants, and antipsychotic drugs.

Lithium Carbonate

Concerns about the use of lithium carbonate can be divided into the following areas: the metabolism of lithium during pregnancy, fetal lithium exposure, teratogenic effects, toxic reactions in the newborn, and breast-feeding.

Both the glomerular filtration rate and the effective renal plasma flow increase during pregnancy to approximately 45% above pregestational rates.[1] During this time, the plasma volume increases by about 50%. Renal lithium clearance increases in parallel with the increase in the glomerular filtration rate during pregnancy, and it may be necessary to progressively increase the intake of lithium to maintain a steady serum lithium concentration. During the postpartum period, a corresponding reduction in the amount of lithium administered is necessary to avoid possible toxic levels.[2,3]

It is important to tailor the dosage to each woman's needs. This is most accurately accomplished by using the minimum effective dose and frequent clinical and laboratory evaluations to ensure the maintenance of therapeutic lithium serum levels. To minimize the risk of toxic effects to the newborn and the mother, some physicians advocate discontinuing lithium therapy immediately before delivery.[4] It can be restarted, if indicated, as the mother stabilizes in the postpartum period.

Fetal blood is presumed to have the same serum concentrations of lithium as are found in the maternal blood.[5,6] There have been reports, however, of lithium toxicity in newborns when the maternal serum levels are below, within, or above the adult therapeutic range at the time of delivery. Symptoms in the infant are nonspecific and usually remit with supportive care.[2] Symptoms of neonatal lithium intoxication include cyanosis, jaundice, hypothermia, lethargy, hypotonia, a poor suck reflex, poor respiratory effort, an absent Moro's reflex, low Apgar scores, and altered thyroid and cardiac function that may take as long as ten days to resolve.[5,7,8(pp57-59)] Other reports have included nephrogenic diabetes insipidus, functional tricuspid regurgitation, congestive heart failure, and atrial flutter.[9-11]

Thyroid effects have also been reported in children born after in utero lithium exposure. Schou and co-workers described one child born with a large goiter that regressed spontaneously and another who was born with reversible hypothyroidism.[12]

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There is no clear evidence to establish lithium's role as a "behavioral teratogen." When children with in utero exposure to lithium were compared at follow-up with sibling controls, there was no significantly increased incidence of physical or mental anomalies in the children with exposure to lithium.[13] Conclusions were based only on the mothers' subjective assessments of their children, however, and not on the results of a physical examination or psychological testing.

The teratogenic effects of lithium are well documented in invertebrate and nonmammalian species.[14] Findings have included head and neck abnormalities, a disruption in the central nervous system development, and abnormal tissue differentiation. In many animal cases, however, serum concentrations exceeded those used in humans.

A "lithium baby register" was established in 1969 to collect information about the effects of lithium on in utero development.[15] By 1978 a high frequency of congenital malformations had been reported.[16] This may represent the tendency of such a method of data collection to overestimate the frequency of problems because clinicians are more likely to report a case in which there have been complications. Of 217 reported cases of exposure to lithium during at least the first trimester, 25 infants were born with congenital anomalies. Of the 25 infants, 18 had cardiovascular malformations, 6 of which involved Ebstein's anomaly of the tricuspid valve, atrial septum, and right ventricle. Based on these data, lithium has been suggested to be a cardiovascular teratogen.[5,17] Although the absolute incidence of malformations reported in the register is no higher than what is found in the general population, the register's data suggest that lithium not be used during the first trimester unless it is absolutely essential.[18]

Breast-feeding is complicated by the fact that the concentration of lithium in breast milk is about 50% of that in a mother's serum.[2] Lithium ingestion during breast-feeding is discouraged because of the concern for the development of toxic effects if there are fluid and electrolyte alterations in the infant, such as dehydration, and because the effect on an infant of ingestion by its mother of subtherapeutic levels of lithium is unknown. The decision to breast-feed should be undertaken only after a fully informed discussion between the parents and the physician. For some parents, the immunologic and psychological advantages of breast-feeding may outweigh the possible risks of lithium therapy.[7]

With the inability to predict exactly the risk associated with lithium use during pregnancy, only general guidelines are available. If lithium therapy is indicated, then the lowest serum levels possible that will provide adequate behavioral improvement should be used, and the total dose should be spread throughout the day, with each individual dose as low as possible.[5] Schou and Goldfield recommend additional guidelines for pregnant women on lithium therapy.[19] Its use should be discontinued for at least a month before pregnancy is attempted. If possible, a patient should be maintained free of lithium throughout the pregnancy. Lithium therapy should be reinstated only when the risk of relapse appears to exceed the possible morbidity of drug use. It should be discontinued, if possible, if a patient becomes pregnant. The woman should be told that many normal infants have been born to mothers taking lithium while pregnant. In addition, it is now possible to follow infant development in utero with such imaging procedures as ultrasonography to monitor the possible development of anatomic congenital anomalies.

Pregnant women are at risk for the same spectrum of adverse reactions as other patients—endocrine, renal, gastrointestinal, neurologic—but the physiologic changes of pregnancy may increase the relative risk.[20]

Antidepressants

Although direct proof of their teratogenicity is lacking, the use of cyclic antidepressant drugs has been associated with an increased risk of birth defects.[7,8,21,22] The results of studies in animals suggest that these agents can act as teratogens.[23] Although the ability of at least imipramine hydrochloride and desipramine hydrochloride to cross the placenta has been shown in both humans and animals,[24,25] in a study of 19 women taking imipramine and 28 women receiving amitriptyline hydrochloride during the first trimester of pregnancy, there was no evidence of congenital malformations.[26] In another study of 15,000 births, there was no evidence of gross congenital abnormalities in infants born to women who received tricyclic antidepressants during the first trimester.[27] From data contained in a register of 2,784 cases of birth defects matched to an equal number of control subjects, the teratogenic potential was estimated to be fairly low even with exposure during the first trimester.[28]

There does appear to be a greater consensus, however, that in the immediate postpartum period, a newborn can show the effects of antidepressants received in utero. There are reports of infants showing signs of respiratory distress, urinary retention, myoclonus, tachycardia, and heart failure.[8,22] Some of these infants have later shown signs of withdrawal.

The use of monoamine oxidase inhibitors should be avoided for several reasons. The possibility of a hypertensive reaction leading to severe vascular difficulties for both the mother and the fetus has been a common concern.[8] In addition, monoamine oxidase inhibitors have been shown to be teratogenic in animals.[29]

Antipsychotic Drugs

Phenothiazine and thioxanthene derivatives have been shown to cross the placenta.[30,31] Most reviews of the effects of neuroleptic drugs have not found a statistically increased incidence of structural birth defects in those infants with in utero exposure. A retrospective examination of 100 women receiving haloperidol while pregnant revealed no notable effect on the sex ratio of offspring, birth weight, intrauterine or neonatal survival, fecundity, or duration of gestation compared with controls.[32] In a review of 341 cases of intrauterine exposure to trifluoperazine hydrochloride, there was no increased incidence of congenital anomalies compared with the general population.[33]

In a prospective study of 12,764 women and their offspring receiving exposure to phenothiazines in the first trimester, a statistically significant increase was found in the incidence of major congenital anomalies when the exposure was to phenothiazine derivatives with a 3-carbon aliphatic side chain: chlorpromazine, methotrimeprazine, trimeprazine tartrate, and oxomemazine.[34] These side effects included malformations of the central nervous, cardiovascular, digestive, musculoskeletal, and genitourinary tract systems. There was a high incidence of microcephaly, ventricular septal defect, cleft lip, hypospadias, polydactyly, and syndactyly. This was not observed with the use of promethazine hydrochloride or the piperidine and piperazine antipsychotic

drugs. Of the drugs suggested by this report to have a deleterious effect, only chlorpromazine is used as an antipsychotic in the United States.

Contradictory findings were reported in a study of 19,952 women treated with phenothiazines during their first trimester. There was no significant increase in the incidence of severe congenital anomaly and perinatal death for the group receiving exposure versus controls.[35]

Toxic effects have been reported in newborns, including restlessness, abnormal movements, hypertonia, and an extrapyramidal syndrome that includes tremor, hypertonia, weakness, and poor sucking and sluggish primitive reflexes.[36-39] This syndrome may be familial and is most likely dose-dependent.[8] Extrapyramidal symptoms in the newborn are reported to persist for as long as six months.[39]

Nonphenothiazine or nonbutyrophenone antipsychotic drugs such as thiothixene, molindone hydrochloride, or loxapine hydrochloride have not been investigated sufficiently to accurately report the incidence of fetal abnormalities associated with their use during pregnancy.

As a generalization about the use of antipsychotic drugs during pregnancy, some authorities have suggested that it is best to avoid their use during the first trimester and to consider their use during subsequent trimesters only under urgent circumstances.[7,8]

Benzodiazepines

Early reports evaluating the effects of benzodiazepine exposure on fetal formation described an increased incidence of malformations such as cleft lip or palate following early fetal exposure.[40] More recent studies have failed to confirm this finding, however.[41] A survey of 19,000 pregnant women also failed to find an increase in the incidence of congenital malformations in babies with exposure to benzodiazepines.[42]

A neonatal abstinence syndrome has been reported in neonates born to mothers who ingested benzodiazepines in the last trimester of pregnancy.[43] It consists of tremor, increased sucking, irritability, and hypertonicity. Depression of the neonatal central nervous system may occur following the administration of benzodiazepines during labor.[44] Its manifestations include hypothermia, apnea, and an impaired suck reflex.

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